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TITLE: Efficacy of Adjunctive Sleep Interventions for PTSD

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14. ABSTRACT Since the last report, we have successfully achieved all goals initially set in our statement of work and task timeline for the first 24 months of the award. Recruitment has been delayed and accrued at a slower pace than initially anticipated for clinician-initiated referrals. However, we have rapidly changed our recruitment strategy and continue to seek opportunities to collaborate effective with our colleagues at the VAPHS to facilitate and enhance recruitment of military veterans with sleep disturbances to our research program. This award has also significantly contributed to other reportable outcomes including several presentations, and provided preliminary data for 2 successful applications for federal funding by the PI.					
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Efficacy of Adjunctive Sleep Interventions in PTSD (PR054093)

Updated Progress Report September 30 2007 to April 22 2008

I. INTRODUCTION.

Sleep disturbances are common and often resistant to first-line treatments of typical mental health disorders and post-deployment adjustment difficulties experienced by veterans who served in combat zones, including posttraumatic stress disorder. Although adjunctive pharmacological or behavioral sleep interventions are often required to adequately reduce nightmares and insomnia in veterans with these psychiatric difficulties, the efficacy and durability of adjunct sleep interventions have not been formally evaluated and compared. The overarching objective of this study is to investigate and compare the efficacy and durability of adjunctive sleep-focused interventions on sleep, daytime symptoms of PTSD, mood, and anxiety in a sample of 90 male and female veterans who experience nightmares and insomnia following military deployment. The proposed study will contribute to the development of effective therapeutic strategies for post-deployment mental health difficulties, and provide novel information regarding predictors of sleep treatment response.

II. BODY.

Research accomplishments associated with each task outlined in the approved Statement of Work.

The tasks and timeline initially proposed and approved since September 2007 in the statement of work is provided here. Progress and outcomes on each of the task listed in Table 1 are detailed below.

Table 1. Proposed Task Timeline	Year 2 (02/16/07 – 04/30/2008)			
	Months 1-4	Months 5-8	Months 9-12	Status
<i>Task</i>				
Subject recruitment & enrollment				Ongoing
Randomization and treatment delivery				Ongoing
Telephone Follow-ups				Ongoing
Data safety and monitoring plan				Ongoing

Task 1: Subject recruitment and enrollment

Recruitment continues to use several venues for recruitment and advertisements, and to explore new ones.

By far, the most fruitful approach for recruitment has been television advertisements. Since the initiation of recruitment in October 2006, we have been contacted by 544 veterans (292 in September 07) veterans, who saw the television advertisement for the study. Television advertisements are more expensive than our original recruitment plan which heavily relied on referral from the local VA clinics, but possible because costs associated with laboratory procedures have been significantly reduced institutionally since funds were awarded.

We continue to attend weekly meetings at the VAPHS PTSD Clinic to consult with clinicians at the OIF/OEF Clinic. The VAPHS now permits to recruit potential participants though clinician-initiated referrals only. Since the initiation of recruitment in October 2006, we have received 53 (11 since September 2007) referrals from the VAPHS. While this is an appreciable number of referral given the work load from clinicians who are not typically involved in research activities of the VAPHS clinics, this is significantly below 3-4 referrals per week initially anticipated by the clinicians at the VAPHS.

The study recruitment flow chart is provided in Appendix I. As shown in the study flow chart, a total of 544 individuals have contacted us, and we were able to reach and initiate the telephone screen with 413, and to complete both the telephone script and screening telephone interview with 213 individuals. All were invited for a consent visit, and 64 provided written, informed consent. Reasons for withdrawal or exclusion at the different study phases are provided in the study flowchart.

Of the 64 participants of provided written, informed consent, 26 have been randomized to Medications (Group 1 in study flow chart; Prazosin or Placebo, n = 18) or to the behavioral sleep intervention (Group 2; n = 8). Reasons for exclusion prior to randomization included obstructive sleep apnea, lack of interest and incompatible time requests, substance use disorder, and severe ongoing psychiatric conditions requiring immediate psychiatric care. (For more detail, please see Appendix I).

Table 2 presents the demographic of the 64 individuals have provided written, informed consent for this study as of April 22 2008. These demographics are consistent with our proposed recruitment plan. Efforts to enroll women have been increased, and we are confident that success in enrolling women in the study will be successful in this funding period, as we will strengthen our collaboration with the VAPHS Women's Health Clinic.

Another initiative targeting recruitment of military veterans involves the development and launch of a website to provide information about the study and about sleep research conducted at the University of Pittsburgh (<http://www.veteranssleep.pitt.edu>). The website is provided in all local advertisement media. Data regarding the number of "hits" per month since

Table 2. Demographic information of participants who have provided written, informed consent as of April 22, 2008.

Ethnic Category	Sex		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	5	58	63
Ethnic Category Total of All Subjects*	5	59	64
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	12	13
White	4	46	50
Racial Categories: Total of All Subjects	5	59	64

September 2007 are provided in Appendix II. Since September 2007, the website had between 700 and 2400 "hits" per month, with increased number of "hits" coinciding with advertisements on public media. 41 individuals contacted us by email or directly via the website. While this reflects a minority of individuals, we are confident that public knowledge about the study is increasing, and that this will translate into a growing number of contacts.

We continue to explore to recruitment venues. For instance, ads have been placed on 70 buses on the Pittsburgh Port Authority. We have also secured IRB approval from the VAPHS to conduct a mass mailing effort to send letters to inform all veterans registered at the PTSD and OIF/OEF clinics of the ongoing studies. The mass mailing is scheduled for June 2008, and over 3,000 veterans will be reached by mail. If mass mailing turns out to be a successful recruitment strategy, we will expand our mass mailing recruitment effort to other VAPHS clinics (e.g., primary care clinics; women's health clinic; audiology; rehabilitation, etc.). The effort is possible because of the support from Dr. Gretchen Haas, Ph.D. director of the VISN 4 MIRECC. The MIRECC will indeed be supporting the costs of the mass mailing.

Task 2: Randomization and treatment delivery

As indicated above, 26 individuals have been randomized (8 to BSI, 18 to medications [prazosin or placebo]), since recruitment began. No deviation to the randomization or treatment delivery protocols has been reported. Unexpected, adverse side effects have not occurred. One participant randomized to medication withdrew his/her participation (randomized to placebo) and 3 participants randomized to medication were withdrawn by the study (2 randomized to prazosin, 1 unknown) and four participants randomized to BSI were withdrawn by the study, as well. Reasons for withdrawal included protocol noncompliance (n= 5), work-related relocation (n = 1), substance abuse (n=1), and side effects (n = 1; randomized to placebo).

Task 3: Telephone Follow-ups

Telephone follow-up have been completed in all participants who completed the intervention phase. Seven participants have completed the entire post-treatment follow-up period, and 12 are currently in the follow-up period.

Task 4: Data safety and monitoring plan

The PI continues to hold and lead weekly team meeting to closely monitor the progress of the study. These meetings are also used to review, verify and achieve consensus on participants' eligibility and safety to participate in the study; verify if any member of team has become aware of the new information that alters the risk/benefit assessment of the present study, verify that confidentiality has been protected and no breach has occurred; and search the literature on new information that may affect the current assessment of the risk/benefit ratio. New literature relevant for the continuous assessment of the risks and benefits are the study is sought weekly, and reviewed when available.

A second Data and Safety Monitoring Board (DSMB) was held on January 16 2008. The DSMB includes Drs. Ellen Frank, Wesley Thompson, and Terry Keane. Summaries of recruitment results, study procedures, and any unexpected/adverse event were provided to the members for review. The DSMB expressed no concerns regarding the integrity of the data, participants' safety, and study procedures. The DSMB report is included with this report, in Appendix III. The next DSMB meeting is scheduled for July 2, 2008, and will include all members.

Problems in accomplishing any of the tasks.

We originally proposed to consent 120 participants, of whom 90 would be randomized and 66 were expected to complete the acute intervention phase. Despite increased recruitment efforts, we are currently experiencing some delay in meeting our initial recruitment plan /goals. Our original projection was to consent and randomized 2.5 participants / month of recruitment over a recruitment period of 36 months. Due to delays in securing all IRB approvals at the onset of the funding period, recruitment was initiated in October 2006, and not in May 2006 as originally planned. Nevertheless, over a period of 18 months of recruitment, we have consented 64 individuals, 19 more than the anticipated 45 participants. As such, we have exceeded our enrollment goal. However, the current available recruitment data indicate that we will need to consent up to twice as many participants than anticipated, or up to 240 participants, in order to randomize 90 participants. Therefore, we will continue to intensify our public recruitment efforts considerably by using television advertisements, bus advertisements, and the launch of the study website. We continue to explore to avenues for recruitment, including a mass mailing effort through local VA clinics, and we will strengthen our relationship with clinicians of the VAPHS Women's health clinic.

KEY RESEARCH ACCOMPLISHMENTS.

None at this time.

REPORTABLE OUTCOMES.

Presentations:

The following presentations regarding the scientific and clinical rationale, design and methods of our ongoing clinical trial and preliminary observations were presented by the PI from since September 2007. These presentations aimed 1) educating the scientific and clinical community involved in the care of military veterans with PTSD about the ongoing clinical trial; 2) promoting the importance of sleep in the re-adjustment process following redeployment to the USA in OIF/OEF service members; and 3) enhancing the visibility of the study to enhance recruitment.

Psychophysiological Correlates and Treatments of Sleep Disturbances in Post-traumatic Stress Disorder. Friday, October 12, 2007. Young Investigator Lecture Series, Western Psychiatric Institute and Clinic.

PTSD and Sleep: What we do and why we do it. Invited Staff Luncheon to the University of Pittsburgh Grants and Contracts Office and Office of Research. March 31, 2008.

A mouse model of sleep disturbances in PTSD: Concept Presentation. Anne Germain, PhD. Multidisciplinary Sleep Conference, February 21, 2008.

Sleep and PTSD Research Program. Anne Germain, Ph.D. CTSI Participant and Clinical Interactions Resources (PCIR) Overview, April 8, 2008 UPMC Montefiore Hospital.

Scientific Presentations at International Conferences:

The following abstracts have been submitted and accepted for oral presentation at the 2008 SLEEP Meeting to be held in Baltimore in June 2008.

- Germain A., Walsh C, Stoll M, Hall M, & Buysse DJ. Objective Sleep Disturbances in Returning Veterans with PTSD: Preliminary Findings. Oral Presentation. Sleep 2008, June 7-12, 2008, Baltimore, MD
- Walsh C, Germain A, & Buysse DJ. Sleep quality and disturbances in Returning Veterans: Preliminary Comparisons with Primary Insomnia and Good Sleepers. Oral Presentation. Sleep 2008, June 7-12, 2008, Baltimore, MD

The two abstracts have been submitted for symposium presentations for the 42nd Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT), to be held in Orlando, FL, in November 2008. Decisions are awaited.

- Germain A. & Buysse B. Brief Behavioral Treatment for Chronic Insomnia in Combat-Exposed Veterans: Preliminary Findings on Acceptability, Barriers to Adherence, and Outcomes. Oral presentation submitted for the 2008 Association for Behavioral and Cognitive Therapies (ABCT). November 2008.
- Germain A., Walsh CM, & Buysse DJ. Objective and Subjective Sleep Disturbances in Returning Veterans: Preliminary Findings. Oral presentation submitted for the 2008 Association for Behavioral and Cognitive Therapies (ABCT). November 2008.

Finally, one research trainee presented a poster on bereavement, grief, and PTSD in returning veterans.

- Stoll MT, Walsh CM, Troxel WM, Germain A. Frequency and effects of bereavement in OIF/OEF military veterans with PTSD. Poster to be presented at the 2008 National Conference for Undergraduate Research (NCUR), at Salisbury University, April 10-12, 2008.

Funding requested and obtained based on work supported by this award:

- Early in the course of our ongoing clinical trial, we have found that a considerable number of military veterans report insomnia related to post-deployment adjustment disorders, but do not meet diagnostic criteria for PTSD. Therefore, we have developed and submitted an R34 proposal aimed at adapting and testing a brief behavioral treatment of insomnia previously developed by our team over the course of another study funded by National Institutes of Mental Health (NIMH) (AG20677). Recruitment data and clinical observations derived from the current clinical trial provided preliminary data for this application. Our NIMH proposal, entitled “Brief Behavioral Treatment of Comorbid Insomnia in Returning Veterans” was favorably reviewed, and funding is awaited pending IRB approval anticipated on May 1, 2008.
- We have just received the notification that our Investigator-Initiated Research Award proposal submitted in response to recent announcements by the Department of Defense for PTSD research (W81XWH-07-PTSD-IIRA) was to be funded through the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury. In this new study (PT073961), we propose to include functional neuroimaging to the ongoing clinical trial. We propose to expand upon personnel and infrastructures set in place for our ongoing clinical trial to create unique opportunities to gather novel insights into a) the neurobiological correlates of PTSD during sleep and of response to sleep treatments. We also propose to explore neurobiological predictors of sleep treatment response across the sleep-wake cycle.
- We have submitted re-submitted an R21 proposal to NIMH in January 2008 aimed at exploring the neurobiological underpinnings of PTSD during REM sleep relative to wakefulness. This proposal is entitled, “*Neurobiological Correlates of REM sleep in PTSD*”, awaits a second review at NIMH, which is scheduled for June 2008. Recruitment data derived from the current clinical trial provided preliminary data for this application.

Research training activities conducted under this award:

- *Elizabeth Shulby, BA, Masters Student in social work (September 2007-April 2008).* Ms. Sheldon completed a research internship required as part of the Masters’ Program in Social Work at the University of Pittsburgh with our research team under the close supervision of the PI and Mr. Abdul Hakim, MSW, the program coordinator. During his internship, Ms. Sheldon assisted the research coordinator in maintaining SOPs and tracking recruitment and enrollment data. She also completed extensive training in the assessment of sleep and psychiatric disorders.
- *Catharine Hebdon, BA, Masters Student in social work (September 2007-April 2008).* Like Ms Shulby, Ms. Hebdon completed a research internship required as part of the Masters’ Program in Social Work at the University of Pittsburgh with our research team under the close supervision of the PI and Mr. Abdul Hakim, MSW, the program coordinator. During his internship, Ms. Hebdon assisted the PI and research coordinator in maintaining SOPs and tracking recruitment and enrollment data. She also completed extensive training in the assessment of sleep and psychiatric disorders.
- *Miriam Stoll* is a student at the University of Pittsburgh, Department of Psychology who completed her undergraduate research project under the supervision of Dr. Germain, between September 2007 and April 2008, she continued to do archival data analysis to evaluate prevalence and severity of grief

symptoms in OIF/OEF and Vietnam veterans using data collected during the screening phase of the ongoing clinical trial. This preliminary analysis indicated that bereavement is highly prevalent in returning veterans and that the severity of daytime PTSD symptoms and of sleep disturbances does not differ in these two cohorts of veterans. These findings were submitted and accepted for a poster presentation at the National Conference for Undergraduate Research (NCUR), at Salisbury University in April 2008.

Since September 2007, all research personnel also completed the following continuing training and education activities:

- *A Window on the Brain*. Giulio Tononi, MD, PhD, Professor of Psychiatry School of Medicine and Public Health University of Wisconsin. Visiting Professorship Lecture. Western Psychiatric Institute and Clinic, February 15 2008.
- *Traumatic Brain Injury VA Medical Center*. Aaron Jacoby, Ph.D. Joint VA-Pitt Lecture Series. Western Psychiatric Institute and Clinic, February 22 2008.
- *Sleep Measurement Workshop*. The research assistant and social work intern attended a day-long training session on the measurement of sleep offered by the Pittsburgh Mind Body Center on April 11, 2008. This one-day training course consisted in an introduction to self-report and objective measures of normal sleep and sleep disorders.
- *Understanding Firewater: Risk Factors for Substance Dependence in Native Americans*. Cindy Ellers, Ph.D. Invited Speaker, Western Psychiatric Institute and Clinic, January 18, 2008.
- *The Statistics of Suicide*. Robert D. Gibbons, PhD, Visiting Professorship Lecture. Western Psychiatric Institute and Clinic, March 28, 2008.

All staff members also regularly attend Grand Rounds presentations held at Western Psychiatric Institute and Clinic on relevant topics, such as assessment and treatment of PTSD in returning veterans, assessment of mild traumatic brain injury, assessment and treatment of anxiety, mood, grief, and sleep disorders, and updates on pharmacological and non pharmacological treatments of anxiety, mood, grief, and sleep disorders. The study therapist, Robin Richardson and Dr. Germain also attended the annual conference International Societies for Traumatic Stress in Baltimore, MD, in November 2007.

CONCLUSIONS

Recruitment and research activities are ongoing. At this point, we have most achieved all goals initially set in our statement of work and task timeline for the first 24 months of the award. Recruitment has been delayed and accrued at a slower pace than initially anticipated for clinician-initiated referrals to the study, but we have intensified our public recruitment methods and continue to explore innovative strategies to further improvement recruitment. No unexpected adverse events have been reported

REFERENCES.

None.

APPENDICES

- Appendix I** Study Flow Chart From October 15, 2006 to April 22, 2008
- Appendix II** Website “hits” from September 2007 to April 2008.
- Appendix III** Report from the Data Safety and Monitoring Board Meeting, January 16, 2008

SUPPORTING DATA.

None provided at this time.

Appendix I
Study Flow Chart (as of 4/22/2008)

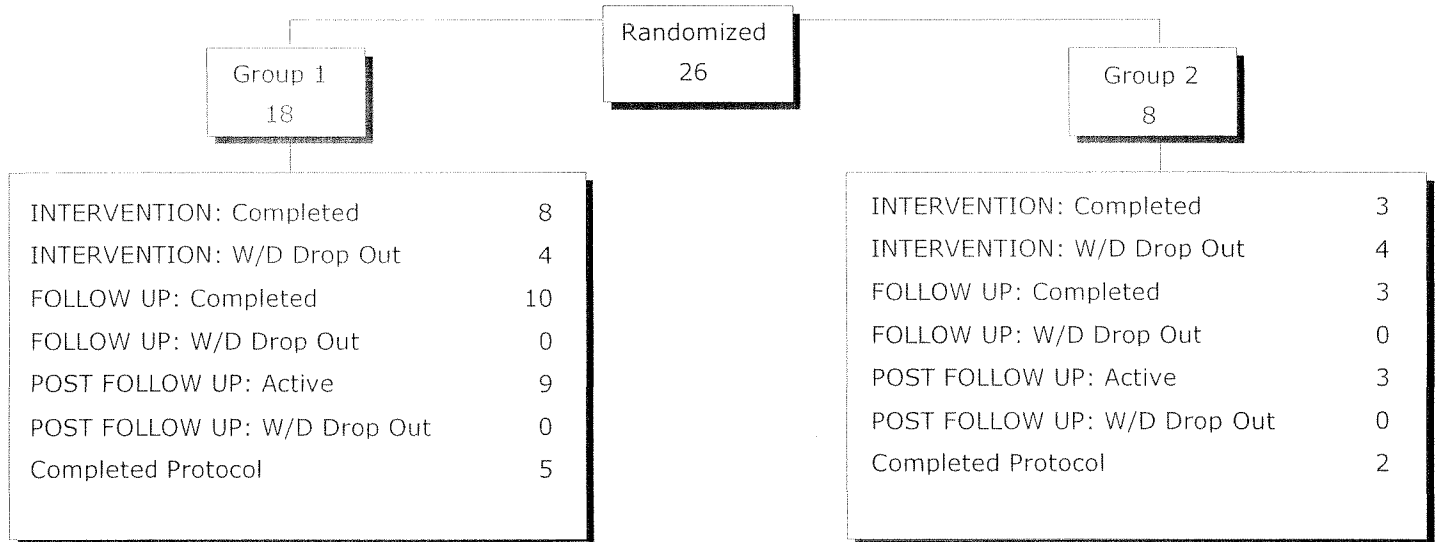
Participant Flow Report for EASIP

Tuesday, April 22, 2008



Participant Flow Report for EASIP


Tuesday, April 22, 2008

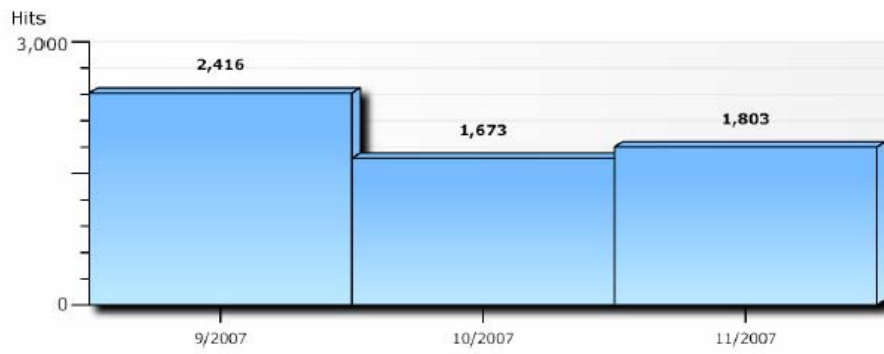



Appendix II

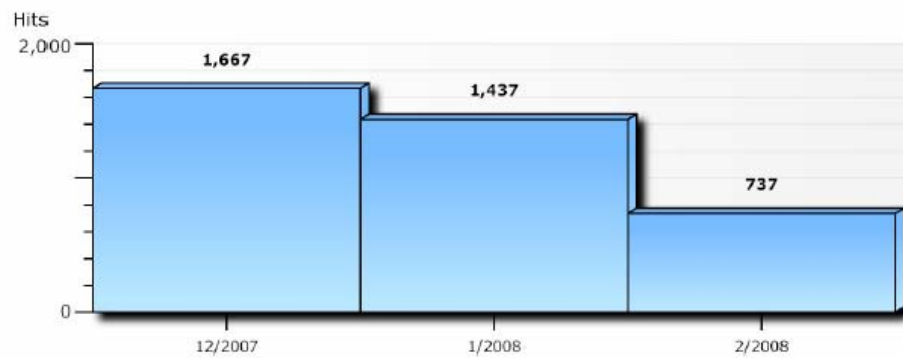
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<http://www.veteranssleep.pitt.edu>

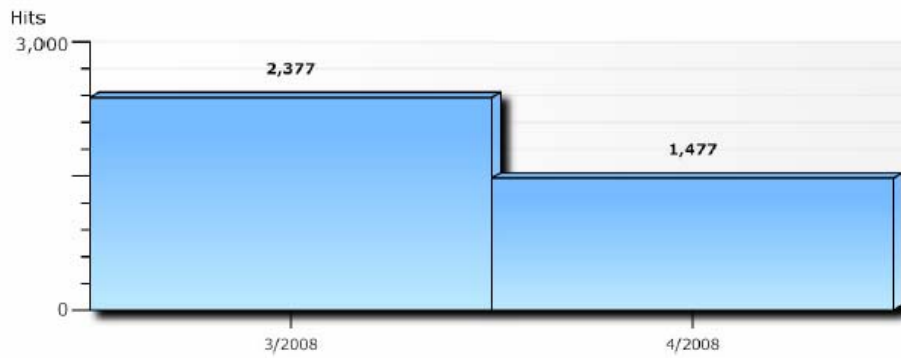
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Date Range: 09/01/2007 - 11/30/2007



 **Report:** Hits Graph
Date Range: 12/01/2007 - 02/29/2008



 **Report:** Hits Graph
Date Range: 03/01/2008 - 04/24/2008



Appendix III

Data Safety and Monitoring Board Report

January 16, 2008



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**Meeting Minutes, Data Safety and Monitoring Board (DSMB)
Efficacy of Adjunctive Sleep Interventions for PTSD (PR054093)**
January 16, 2008

DSMB members: Drs. Wesley Thompson, Ph.D. (Chair), Ellen Frank, Ph.D., Terrence Keane, MD, (via telephone conference)

In attendance: Anne Germain, Ph.D. (PI), Douglas Moul, MD (Co-I), Abdul Hakim (Program Coordinator), and Colleen Walsh (Research Specialist)

Important dates for this study were presented and reviewed by Dr. Germain.

1. Funding start date: February 16, 2005
2. Recruitment projected start date: October 1, 2006
3. Recruitment actual start date: October 1, 2006
4. Recruitment proposed end date: April 30, 2009
5. Recruitment projected end date: August 2009
6. Funding end date: February 15, 2010

The status of the study on the following items, and since the prior DSMB meeting, was then presented and reviewed.

Several changes have been made in response to the DSMB of April 2007 and were reviewed by Dr. Germain. The outcomes of these changes in facilitating recruitment were also discussed. Those included: Removal of the original criterion for meeting PTSD diagnosis; Removal of the original criterion for stable use of an SSRI and duration of the treatment on antihypertensive medications; expansion of the assessment of trauma history. Questions and issues were brought forth regarding the changes. Dr. Thompson asked how making these changes will affect the scientific goals of the study. Dr. Germain responded that does not think the goals will be affected as the primary study goals target sleep disturbances, and not PTSD per se. This also facilitate recruitment because sleep disturbances affect a majority of veterans, regardless of PTSD status.

Updates were provided regarding recruitment to date. The study has achieved a 7-fold increase in recruitment since April 2007. This increase is mainly due to expanded recruitment efforts via television advertisements, and growing staff to ensure prompt contacts with potential research participants. Several subjects who complete a telephone screen are not consented. Dr.

Thompson asked Dr. Germain how will handle the drop-outs at this stage of recruitment. Demographic information collected during the telephone script (age, sex, and race), recruitment source, and exclusion reasons are kept on file and will be analyzed to address this question. This information will also be provided to the DSMB members for the next DSMB meeting.

Recruitment and retention of minorities in the study is low. The study may be successful at reaching minority participants, these often get excluded during the screening process. Most minority subjects to date are African-American Vietnam veterans. Dr. Germain explained that most minority participants were excluded due to medical comorbidities, and especially high blood pressure medications. Dr. Keane concurred that hypertension in African Americans also limits minority research participants in Mississippi and Boston because of the high prevalence of these conditions in African American male veterans. Dr. Frank also noted that Pittsburgh has one of the lowest minority representations (about 18% for the county). For an accurate targeted enrollment of minority participants, Dr. Germain will obtain minority demographics from the VA clinics to compare recruitment figures for the next meeting.

Recruitment of women into the study is also low at this point in time. Dr. Germain noted that in Western PA, only 10% of veterans are women, and acknowledged that current recruitment figures do not meet this demographic information. The investigators will pursue more assertively pursue collaborations with clinicians at the VA Women's Health Center to increase recruitment of women.

There has been no Adverse Events or Serious adverse events (SEs) to do. A list of deviations to the study protocol was reviewed. Deviations are minor and mostly related to delays to the timeline of the study participation to accommodate participants' schedule. One deviation occurred when the blind was broken prematurely. As a result, non-blinded pharmacy titration memos are no longer kept in the participants' binders.

Dr. Thompson will also visit the research team's data entry and manager to review our Access-based database system.

At the conclusion of this review, the DSMB members recommended that:

1. Investigators should specifically target more recruitment sources with African Americans and other minorities including mass advertisements, presence and recruitment at the Kingsley Center, and mass mailings through VA clinics.
2. Investigators should pursue more assertively collaborations with clinicians at the VA Women's Health Center to increase recruitment of women, and investigate whether there are groups of women veterans gather outside of the VA system;
3. Investigators should consider using advertisements on buses (inexpensive and can target bus routes that serve the local VA clinics);
4. Investigators should provide an evidence-based cost estimate of recruitment costs / randomized subjects;
5. Investigators should provide available information related to the performance of the study website;

6. Investigators should provide the detailed table that includes all demographics and clinical data per randomized group;
7. Investigators should also provide more detail on the randomization outcomes to date to provide evidence that it is balanced for age, gender, medications, CAPS scores;
8. Investigators should also include as much information as available regarding withdrawals after screening, drop-out rates, and withdrawals (subject- or investigator-initiated) after the randomization, including a breakdown of participants who dropped out against the study's medical advice versus those who dropped out as per the study's consensus;
9. The monthly projections and goals for recruitment should be recalculated and adjusted at the current recruitment rate.

The next DSMB meeting will be held in June 2008. The time and date will be determined by email communication later this month.

A handwritten signature in black ink, appearing to read 'Wesley Thompson', with a stylized, flowing script.

Wesley Thompson, PhD
DSMB Chair
Assistant Professor of Statistics and Psychiatry
University of Pittsburgh